

REMARKS/ARGUMENTS

Claim 12 is canceled without prejudice. Claims 1, 11, 13, 23, and 31 are amended. The support for amendment of claim 1 can be found on page 3, lines 24-31 of the specification. The support for amendment of claim 11 can be found in Example 12, pages 47-49, of the specification. The support for amendment of claim 1 can be found on page 3, lines 24-31 of the specification. The subject matter of claims 13, 23, and 31 has not been changed. New claims 72-79 are added. The support for claim 72 can be found in Example 12, pages 47-49, of the specification. The support for claim 73 can be found in the original claim 31. The support for claim 74 can be found on page 3, lines 24-31 of the specification. The support for claim 75 can be found on page 25, lines 27-31 of the specification. The support for claims 76-79 can be found in the original claims 3, 6, and 23. No new matter has been introduced. Claims 1, 3, 6-7, 10, 11, 13-23, 30-31, and 72-79 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

Claim Rejection Under 35 U.S.C. § 112:

Claims 1, 3, 6, 7, 10-23, 30 and 31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, claim 1 is rejected for the use of the term "predicting." This rejection is respectfully traversed.

The Examiner deemed the term "predicting" to be a relative term, which is not supported by the specification because "the specification does not provide a standard for ascertaining the requisite degree." The Examiner also noted that the term makes claim 1 unclear with respect to whether the method includes "determining a disease before it actually occurs." Applicants disagree.

The term “predicting” is fully supported by the instant specification. The methods of the present invention are directed to both diagnosis of an existing disease and prognosis (or prediction) of a future development of a disease (page 28, lines 7-15 and 22-23; page 37, lines 3-6; and Example 12 on pages 47-49). Although applicants believe that the language of the original claim 1 is clear, in order to expedite the prosecution of the instant application, applicants have amended claim 1. The amended claim 1 explicitly states that the determined content of a component of the isolated mucin can be used to either diagnose an oral disease or to predict its future development.

The Examiner rejected claims 11-13 as vague and indefinite for the use of the phrase “risk of said disease as high, medium, or low” in claim 11 without specifying values that define high, medium, or low risk. This rejection is moot with respect to claim 11 due to the deletion of the objected phrase from the claim. New claim 72 provides the ranges for high, medium, or low risk as suggested by the Examiner.

The Examiner rejected claim 31 as indefinite and ambiguous for the recitation of the abbreviations DFT, DMT, and DMFS. This rejection is moot with respect to claim 31 due to the deletion of the objected abbreviations from the claim. New claim 73 defines the abbreviated terms as suggested by the Examiner.

Accordingly, applicants respectfully request a withdrawal of the rejection of claims 1, 3, 6, 7, 10-23, 30 and 31 under 35 U.S.C. § 112, second paragraph.

Claim Rejection Under 35 U.S.C. § 102:

Claims 1, 7, and 14-19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Nielsen *et al.*, Journal of Dental Research, Vol. 75, No. 11, pp. 1820-1826, 1996 (Nielsen). This rejection is respectfully traversed.

Nielsen does not anticipate claim 1, which is directed to diagnostic and prognostic method for oral diseases. Amended claim 1 requires a step of

quantitating the content of a component of isolated mucin to diagnose or to predict a future development of an oral disease. The claim limits oral diseases to *dental caries, periodontal diseases, mucosal infections, oral and pharyngeal cancers and precancerous lesions*, and their combinations. Nielsen does not teach any of the listed diseases. Instead, Nielsen describes detection of a mucin in concentrated saliva with antibody probes and notes that “[t]he development of these antibody probes will facilitate studies of mucin expression in *diseases of salivary glands*” (Abstract).

Nielsen does not suggest the independent claim 1. It is a discovery of the instant invention that a strong correlation exists between the amount of a component of an isolated mucin (such as sialic acid associated with MUC7 mucin) and a presence or a risk of development of an oral disease (such as dental caries) (page 34, lines 25 –page 36, line 22). As explained on page 2, lines 3-8, of the specification, prior to the instant invention, there was no consistent evidence of correlation between mucin in saliva and oral diseases. The present invention demonstrates such a correlation and, thus, the present invention provides unexpected results.

Nielsen has no teaching whatsoever of a correlation between a concentration of a component associated with an isolated mucin and an existence or a risk of oral disease, much less of such correlation where the oral disease is selected from a group consisting of dental caries, periodontal diseases, mucosal infections, oral and pharyngeal cancers and precancerous lesions, and their combinations. Since unexpected results are obtained in the present invention, a mere mentioning of antibody probes for mucin and their use to facilitate studies of mucin expression in diseases different than those listed in claim 1 does not make the amended claim 1 obvious.

Therefore claim 1 is patentable over Nielsen. Claims 7, and 14-19 depend, directly or indirectly, from claim 1 and are, therefore, patentable over Nielsen for at least the same reasons as claim 1.

Claim Rejection Under 35 U.S.C. § 103:

Claims 3, 6, and 23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nielsen in view of Belce *et al.*, Tohoku Journal of Experimental Medicine, 11/2000, Vol. 192, No. 3, pp. 219-225, Abstract Only (Belce). This rejection is respectfully traversed.

As discussed above, claim 1 is patentable over Nielsen. Belce does not overcome the defects of Nielsen and is not cited by the Examiner for such. The Examiner cites Belce for describing that decreased levels of salivary sialic acid may be a possible factor leading to oral complications of *diabetis* mellitus. However, there is nothing in Belce that indicates a correlation between salivary sialic acid and *specific oral diseases* of claim 1, such as dental caries, periodontal diseases, mucosal infections, oral and pharyngeal cancers and precancerous lesions, and their combinations.

Additionally, Belce assess total sialic acid level in saliva, *not sialic acid associated with isolated mucin* as required in the instant claim 1. As discussed above, it is a discovery of the present invention that the severity of an oral disease, such as dental caries, correlates with the *sialic acid concentration associated with mucin* in saliva (page 34, lines 25-26, and page 36, lines 19-22). This discovery advantageously allows to detect preexisting oral diseases and to predict a future occurrence of oral diseases by measuring a concentration of a component, such as sialic acid, associated with isolated mucin. Accordingly, claim 1 of the instant invention requires isolation of mucin and determination the content of a component associated with the isolated mucin. The determination of total sialic

acid in saliva described by Belce would not have motivated those skilled in the art to isolate mucin and determine sialic acid in the isolated mucin.

Finally, even with respect to oral complication of diabetes and total sialic acid, Belce does not describe a definite correlation between these two variables. Belce merely indicates that “decline *both* in sialic acid and [Superoxide Dismutase] *SOD* in saliva *may be a possible factor* leading to oral complication of diabetes.” Belce teaches that both sialic acid and SOD may contribute to oral complication of diabetes, but Belce does not provide any data demonstrating a definite correlation between *sialic acid alone* and oral complication of diabetes. Thus, Belce does not make the correlation discovered in the present invention obvious.

Therefore, claim 1 is patentable over Nielsen in view of Belce. Claims 3, 6, and 23 depend from claim 1 and are, therefore, patentable over Nielsen in view of Belce for at least the same reasons as claim 1.

Claims 10, 11-13, 20-22, and 30-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nielsen in view of Belce and in further view of Astor *et al.*, Ear, Nose & Throat Journal, 7/1999, 78(7), pp. 476-479 (Astor). This rejection is moot with respect to claim 12 due to the cancellation of the claim. With respect to claims 10, 11, 13, 20-22, and 30-31, the rejection is traversed.

As discussed above, claim 1 is patentable over Nielsen in view of Belce. Astor does not remedy the defects of Nielsen and Belce. Contrary to the Examiner's view, Astor does not teach evaluating mucin levels in saliva to assess a risk of “dental caries disease such as Xerostomia.”

First, Xerostomia is not a caries disease, but rather a risk factor of developing caries disease. In this regard, applicants respectfully draw the Examiner's attention to page 478, right column, the first paragraph of Astor (under the heading “Dental Complications of Xerostomia” of the '282 patent). Astor describes a dry mouth condition that may “alter the oral flora and *contribute to plaque*

formation, thereby increasing the risk for opportunistic infections ... and the proliferation of cariogenic microorganisms" and weaken "dentition's defense against caries."

Second, Astor has no teaching whatsoever of a correlation between a concentration of mucin in saliva and a risk of dental caries. Astor only states that xerostomia places patients at risk of caries (abstract) by contributing to the plaque formation (see above) and that aging may result in significant changes in saliva's composition, including a decrease in ptyalin and an increase in mucin (page 477, left column, last paragraph immediately above heading "Prevalence and Associated Causes"): Thus, at the most, Astor indicates that xerostomia can be accompanied by an increase in mucin. Based on these teachings, those skilled in the art would not have realized that content of mucin in saliva directly correlates with a risk of caries or other oral diseases.

Therefore, claim 1 is patentable over Nielsen in view of Belce and in further view of Astor. Claims 10, 11, 13, 20-22, and 30-31 depend from claim 1 and are, therefore, patentable over the cited references for at least the same reasons as claim 1.

Applicants added new independent claims 75 and 77 to better define the scope of the invention. The support for claim 75 can be found on page 25, lines 27-31 of the specification. The support for claims 77 can be found in the original claims 1 and 3.

Claim 75 is directed to a diagnostic and prognostic method comprising the steps of: a) providing a saliva sample from a subject; b) *isolating a mucin from all other sialic acid-containing molecules* in said saliva sample to produce an isolated mucin; and c) measuring an *amount of sialic acid associated with the isolated mucin* to diagnose or to predict a future development of a disease in said subject. This claim is patentable over the cited references, taken alone or in a

combination, because the references do not teach or suggest measuring an ***amount of sialic acid associated with the isolated mucin.***

Claim 77 is directed to a diagnostic and prognostic method comprising the steps of: a) providing an ***unstimulated saliva*** sample from a subject; b) isolating a mucin to produce an isolated mucin; and c) quantitating the content of ***a component of said isolated mucin*** to diagnose or to predict a future development of a disease in said subject. This claim is patentable over the cited references, taken alone or in a combination, because the references do not teach or suggest quantitating the content of ***a component of the mucin*** isolated from ***unstimulated saliva.***

New claims 72-74, 76, and 78-79 depend, directly or indirectly from patentable claims 1, 75, and 77 and are, therefore, patentable over the cited references for at least the same reasons as claims 1, 75, and 77.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,

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